Docket No.: 13796-00002-US
(Patent)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Li, Guoqiao et al.

Application No.: 10/587,277 Confirmation No.: 4870

Filed: July 25, 2006 Art Unit: 1616

For: COMPOUND ARTEMISININ Examiner: Arnold, Ernst V

1.132 SUPPLEMENTAL DECLARATION

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

1. We, Guoqiao Li and Jianping Song are citizens of China and reside at Guangzhou, China, hereby declare and say as follows:

2. Our individual resumes are appended hereto as part of this Declaration showing our qualifications related to the subject matter of the present invention.

3. This Supplemental Declaration provides additional information and supplements our first Declaration which we executed and we understand was filed in this matter.

4. We are the named inventors of application, U.S. Application No.: 10/587,277 ('277 Application).

5. We have read and reviewed the '277 Application and the Examiner's comments in the official action dated 05/08/2009.

6. We conducted clinical trials to treat patients with malaria and compared the present formulation of the '277 application (described below) with the reference formulation of dihydroartemisinin and piperaquine phosphate (also described below) for the percent

incidence (%) of various side effects and for efficacy.. The results and statistical analyses are set forth in table 1 below.

Table 1. Comparison of the side effects of the present formulation with those of the reference formulation

Side effects	The present Formulation [1]	The reference Formulation [2]	X^2 value	P value [3]
reduced appetite	1.4%	2.8%	0.6899	0.4062
nausea	3.2%	6.6%	4.2488	0.0393
vomiting	2.1%	6.6%	8.0549	0.0045
diarrhea	1.0%	2.8%	1.8055	0.1790
abdominal pain	1.0%	1.9%	0.2497	0.6173
headache	0.8%	2.8%	2.4363	0.1186
dizziness	1.4%	4.7%	5.7108	0.0169
insomnia	0.6%	2.8%	3.2886	0.0698
tiredness	0.6%	0.9%	0.0368	0.8478

7. In Tables 1 and 2, the present formulation contains in each tablet artemisinin 62.5 mg, piperaquine 312.5 mg, and primaquine 2 mg.

8. In Tables 1 and 2, the reference formulation contains in each tablet, dihydroartemisinin 40 mg, and piperaquine phosphate 320 mg.

9. Statistical tests were performed and as summarized in Table 1. The x^2 test (2x2) values and the ; P values < 0.05, show significant differences between the side effects observed for the present formulation as compared with the reference formulation at comparable efficacies. Thus we conclude that the present formulation is safer than the reference formulation.

10. Table 2, below shows the dosage levels for the present and reference formulations.

Table 2. Comparison of administration of the present formulation with the reference formulation for one treatment period

	Administrated doses (tablet)				Total dose
Formulation	0 hour	8 hours	24 hours	32 hours	(tablet)
The present formulation	2		2		4
The reference formulation	2	2	2	2	8

11. As can be seen from Table 2, the total dose of the present formulation for one treatment period is four (4) tablets (1750 mg total), while the total dose of the reference formulation for one treatment period is eight (8) tablets(2880mg total). Such dosing is required to obtain about the same level of treatment or efficacy against the malarial infection. The formulation of the present invention permits dosing to be complete in a shorter time of 24 hours with a total of 4 tablets while requiring 32 hours and 8 tablets with the reference formulation to obtain the same level of treatment of the malarial infection. Thus, the discomfort of the patient is significantly reduced with the formulation of the present invention.

12. The clinical trials that resulted in the collection of data as summarized in Table 1 according to the dosing administration of Table 2 and the formulations described herein, were conducted in multiple centers. The total numbers of patients suffering from pernicious malaria without complications that were treated according to the present formulation were 718 and 106 for the reference formulation.

13. The curative rates when dosing according to the present formulation were 97.7 % for the present formulation and 98.2 % for the reference formulation. Both curative rates are high, satisfactory, and for practical purposes about the same in respect to successfully treating the malarial infection. The results are statistically and practically significant for the treatment of patients afflicted with malaria. The results demonstrate shorter and more cost effective control of malaria with the present formulation with significantly less discomfort to the treated patients as compared with the reference formulation.

14. The beneficial and desirable results and treatment according to the present invention are unexpected in view of the cited prior art and could not have been predicted. It could not be predicted that the advantageous formulation which we discovered would permit effective control is significantly less duration of dosing employing, for example, about one-third less of the present formulation than the reference formulation. This resulted in significantly less side effects and patient discomfort than the prior reference sample. Administration according to the formulation of the present invention has important

practical significance and benefits for the treatment of patients afflicted with malarial infections which is a major problem in many parts the world.

15. For these reasons the applicants believe the formulation and administration of the present invention are not obvious from the prior art.

16. We hereby declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon

Guoqiao Li — October 12, 2009 Date

Jianping Song — October 12, 2009 Date